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Clinicopathological Profile of Invasive Breast Cancer Based on the Human Epidermal Growth Factor Receptor 2 (HER2) at Dr. Cipto Mangunkusumo Hospital from 2019-2020

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ABSTRACT

Introduction
Invasive breast cancer (IBC) is the most common malignancy in women. There are three groups of HER2-negative IBC which are HER2-null (score 0), HER2 ultra-low (score between 0 and 1+), and HER2-low (score of 1+ and 2+ without HER2 amplification). Recent studies on drugs for HER2-negative IBC suggest that the HER2-low and HER2 ultra-low groups with metastasis have the opportunity to receive new therapies, although the ultra-low group is still under investigation. Until now, studies on the three groups of HER2-negative IBC in Indonesia have been challenging to obtain. This retrospective study aims to assess the number of cases in the three groups of HER2-negative IBC and their clinicopathological characteristics at the Anatomical Pathology Department of Dr. Cipto Mangunkusumo Hospital during the years 2019-2020 and to evaluate the discrepancies in HER2 scores after reclassification.

Methods
This is a descriptive study with a cross-sectional design. The study utilizes secondary data from the Department of Anatomical Pathology archives of Dr. Cipto Mangunkusumo Hospital and its electronic medical records. Sample selection was done using consecutive sampling. Clinicopathological characteristics were recorded, and HER2 expression was reassessed and reclassified.

Results
A total of 1129 samples were obtained. The number of HER2-negative cases in the HER2-null group was 352 cases (31.3%), HER2 ultra-low was 214 cases (18.9%), and HER2-low was 563 cases (49.8%). The most common histopathological type of breast cancer and histological grade were no special type (NST) carcinoma and histological grade 2. The most common molecular subtype was luminal B HER2-negative.

Conclusion
HER2 status examination in breast cancer is useful for treatment. Pathologists are expected to distinguish between HER2 scores of 0 and 1+ and to include these in the examination report. This aims to assist clinicians in determining the appropriate therapy for patients.

Keywords: Invasive breast carcinoma, HER2-negative, clinicopathological

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INTRODUCTION

Breast cancer, also known as invasive breast carcinoma, was the second most common malignancy globally in 2022, with an estimated 2.3 million new cases. It ranks fourth in cancer mortality worldwide, with 666,000 deaths (6.9% of all cancer-related deaths). Among females, breast cancer is the most frequently encountered malignancy.[1]

Invasive breast cancer (IBC) can be classified based on molecular subtypes. One such molecular subtype is IBC with overexpression of the human epidermal growth factor receptor 2 (HER2). HER2, or c-erbB-2, is a gene located on chromosome 17 q12-21.32. This gene is part of the epidermal growth factor receptor (EGFR) family and plays a crucial role in cell communication through receptor tyrosine kinases. HER2 is a proto-oncogene that regulates cell invasion, apoptosis, and proliferation. HER2-positive IBC occurs due to HER2 amplification, accounting for 15-20% of cases.[2-4]

HER2 overexpression can be detected through various tests. HER2 protein expression is evaluated using immunohistochemistry (IHC) staining, and HER2 gene amplification is assessed using in situ hybridization (ISH).[5,6] Since 2007, the American Society of Clinical Oncology (ASCO) and The College of American Pathologists (CAP) have established a scoring system for diagnosing HER2-positive IBC. This scoring system includes 0, 1+, 2+, and 3+ scores. The score reflects the level of HER2 protein produced by tumor cells, especially in HER2-negative IBC. Parameters assessed include staining intensity, completeness of staining on the tumor cell membrane, and the extent of the tumor area stained. HER2-negative IBC is characterized by scores of 0, 1+, and 2+ without HER2 amplification, while HER2-positive IBC is defined as a score of 2+ with HER2 amplification or 3+. The result is considered equivocal in cases of HER2 score 2+ from IHC. ISH can be used to confirm whether HER2 amplification is present in these cases.[6]

HER2-positive IBC is treated with anti-HER2 drugs like trastuzumab, while HER2-negative IBC patients do not have a specific treatment. The DESTINY-Breast-04 study tested a new anti-HER2 antibody-drug conjugate (ADC), trastuzumab deruxtecan (T-Dxd), on patients with HER2-low IBC who had metastasized. This drug significantly improved overall survival and progression-free survival by 50% compared to chemotherapy. HER2-low IBC includes those with HER2 scores of 1+ and 2+ without HER2 amplification, while HER2 ultra-low IBC includes scores between 0 and 1+. HER2-low IBC accounts for 40-60% of breast cancer cases. Data on the prevalence of HER2-low and ultra-low groups in Indonesia, particularly Jakarta, is still scarce.[7-9] HER2 assessment is crucial for determining therapy and prognosis. The distinction between IHC HER2 scores of 0 and 1+, previously clinically irrelevant, has become increasingly important and suggests a need for reclassification between HER2-null (score 0) and HER2-low.[10] No additional tests can differentiate between HER2 scores of 0 and 1+. Therefore, accurate diagnosis of these HER2 scores requires expertise from a pathologist.

This study was conducted to determine the number of HER2-negative IBC cases (null, ultra-low, and low) and their clinicopathological profiles at the Department of Anatomical Pathology of Dr. Cipto Mangunkusumo Hospital for the years 2019 to 2020. Additionally, the study aimed to identify the number of HER2-negative cases without documented HER2 scores and changes in HER2 scores before and after reclassification. The findings are expected to provide pathologists and clinicians with information on the magnitude and characteristics of these HER2-negative IBC groups.

METHODS

This retrospective review is a descriptive study with a cross-sectional design. The study uses secondary data from the Department of Anatomical Pathology archives of Dr. Cipto Mangunkusumo Hospital, and its electronic medical records. The target population for this study includes all cases of HER2-negative IBC diagnosed at the Department of Anatomical Pathology of Dr. Cipto Mangunkusumo Hospital during the two years (2019–2020). Inclusion criteria are all HER2-negative IBC cases (HER2 scores of 0, 1+, 2+ with ISH negative) that underwent histopathological and immunohistochemical examinations at the Department of Anatomical Pathology of Dr. Cipto Mangunkusumo Hospital from 2019 to 2020. Exclusion criteria are cases lacking HER2 slides and/or HER2 slides that could not be assessed.

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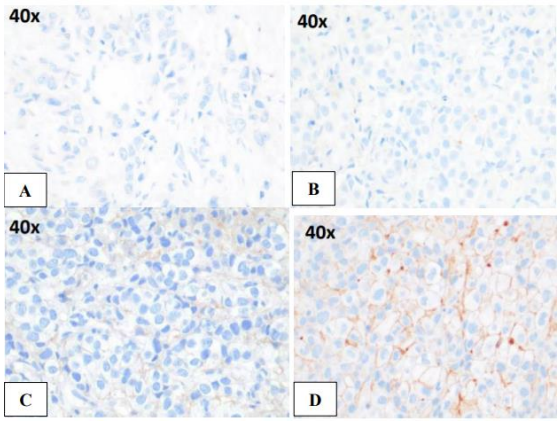

Figure 1 HER2 IHC staining (40 times objective). A. HER2 score 0. B. HER2 score between 0 and 1+. C. HER2 score 1+. D. HER2 score 2+ without amplification.[11]

Sample selection was carried out using consecutive sampling. A total of 1129 cases meeting the inclusion and exclusion criteria were analyzed. Researchers and supervisors performed HER2 assessment and reclassification into HER2-null, HER2 ultra-low, and HER2-low categories (Figure 1). HER2 slides were evaluated in invasive tumor areas, and staining was compared with external controls to avoid false positives and negatives. Data on clinicopathological profiles were collected for all samples.

Detailed tabulation was also performed on histological types (special-type carcinoma, non-special type carcinoma, and mixed carcinoma) and histological grades (grades 1, 2, and 3). The collected clinicopathological data include age, lesion site, lesion size, clinical stage, multifocality, type of surgery, hormone receptor status, Ki-67 status, and tumor molecular subtype. The research flowchart can be seen in Figure 2. The data obtained were statistically processed.

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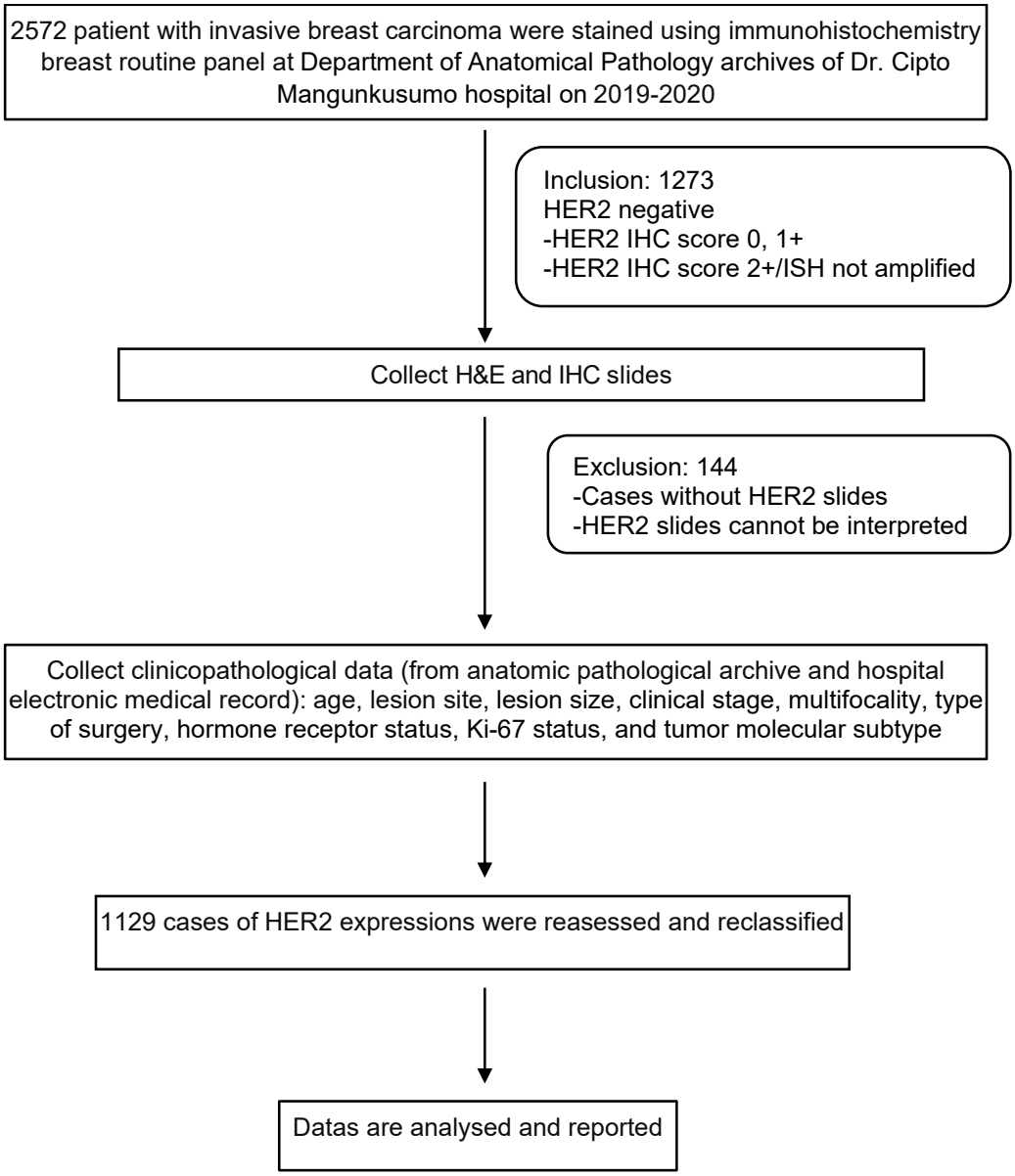

Figure 2. Research flowchart

STATISTICAL ANALYSIS

Based on the archives of the Anatomical Pathology Department of Dr. Cipto Mangunkusumo Hospital from January 2019 to December 2020, 1129 cases of HER2-negative breast cancer met the inclusion and exclusion criteria. The clinicopathological characteristics and histopathological types according to the WHO 2019 classification of the cases included in this study can be seen in Table 1. There were 352 cases (31.3%) of HER2-null, 214 cases (18.9%) of HER2 ultra-low, and 563 cases (49.8%) of HER2-low out of a total of 1129 cases (Figure 3). Some clinicopathological variables such as lesion site, lesion size, multifocality, clinical stage, Ki-67 status, and type of surgery could not be fully obtained. The amount of incomplete data reached 70%, particularly for multifocality and clinical stage variables.

The median age of the study sample was 49 years old, ranging from 22 to 88 years old. There was no median age difference among HER2-null, ultra-low, and low groups. Lesion sites in the three HER2-negative groups did not differ significantly between the right and left breasts, with most lesions (49.1%) found in the right breast. The average

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lesion size was 4 cm, with the largest size being 18 cm in the HER2-null group and the smallest size being 0.8 cm in the HER2 ultra-low group. Breast lesions, both single and multiple, were most frequently found in the HER2 ultra-low group, with single lesions at 19.6% and multiple lesions at 2.8%. Most patients (31.2%) underwent a mastectomy, and 9.8% underwent biopsy.

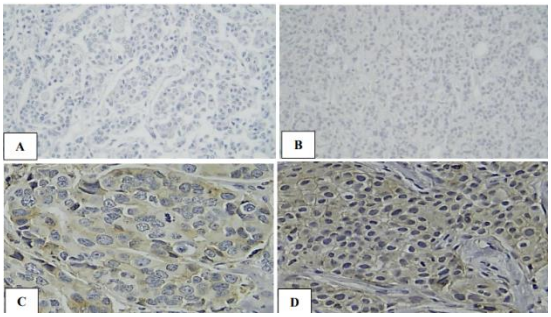

Figure 3. HER2 IHC staining (400 times). A. HER2-*null* B. HER2 *ultra-low* C. HER2-*low* score 1+ D. HER2-*low* score 2+ without amplification.

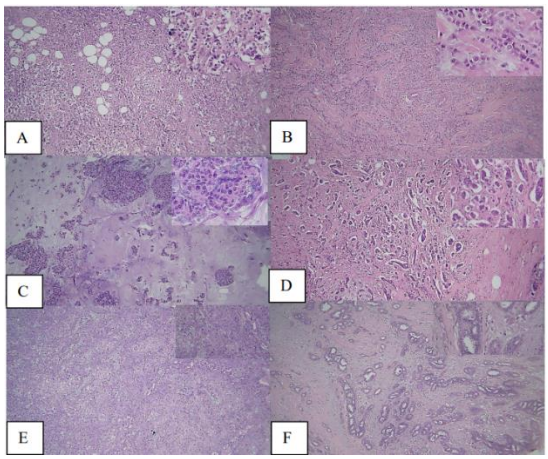

Figure 4. Invasive breast carcinoma histologic type (100 times), inset (400 times). A. NST carcinoma B. Lobular carcinoma C. Mucinous carcinoma D. Micropapillary carcinoma E. Metaplastic carcinoma F. Cribriform carcinoma

Among all cases, the most frequently found histopathological type was NST breast carcinoma, with 287 cases (81.5%) in the HER2-null group, 182 cases (85.1%) in the HER2 ultra-low group, and 462 cases (82.1%) in the HER2-low group. Mixed-type breast carcinoma was the least commonly found, especially in the HER2 ultra-low group at 4.7% (n=10). In addition to NST carcinoma, some special-type carcinomas found in this study included lobular carcinoma, mucinous carcinoma, micropapillary carcinoma, metaplastic carcinoma, and cribriform carcinoma (Figure 4).

Histological grade 3 was most common in the HER2 ultra-low group, at 40.6% (n=87). Histological grade 2 was most common in the HER2-null group, at 53.9% (n=190). Histological grade 1 was most common in the HER2-low group, at 8.2% (n=46). The majority of HER2-negative cases examined at the anatomical pathology laboratory of Dr. Cipto Mangunkusumo Hospital were from patients with advanced stages (stages 3 and 4). The highest number of stage 3 cases was found in the HER2-low group at 16.9% (n=95), and the highest number of stage 4 cases was found in the HER2 ultra-low group at 11.2% (n=24). Hormone receptor-positive tumors were found in all three HER2-negative groups, with HER2-null, ultra-low, and low groups having 75.2% (n=265), 90.6% (n=194), and 87.2% (n=491) respectively. Tumors with high proliferation (Ki-67 ≥20%) were most common in the HER2-null group, at 51.4% (n=181), whereas tumors with low proliferation (Ki-67 <20%) were most common in the HER2-low group, at 52.7% (n=297). The number of HER2-negative cases with luminal A molecular profile was 40.1%, luminal B HER2-negative was 40.5%, and TNBC was 16.7%. Among all HER2-negative cases with the luminal A molecular subtype, 44.8% (n=96) were found in the HER2 ultra-low group, 40.1% (n=141) in the HER2-null group, and 38.3% (n=216) in the HER2-low group. Luminal B HER2-negative subtype cases were 46.8% (n=264) in the HER2-low group, 39.7% (n=85) in the HER2 ultra-low group, and 30.9% (n=109) in the HER2-null group. TNBC subtype cases were 26.1% (n=92) in the HER2-null group, 13.4% (n=76) in the HER2-low group, and 9.8% (n=21) in the HER2 ultra-low group.

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Table 1. Clinicopathological characteristics of invasive breast carcinoma based on HER2 status.

Variable	HER2-*null*		HER2 *ultra-low*		HER2-*low*	
	n=352	%	n=214	%	n=563	%
Age, Median (min-max)	49 (25-80)		49 (22-86)		49 (25-88)	
Site						
Right	161	45.7	105	49.1	259	46.0
Left	160	45.5	91	42.5	255	45.3
No data	31	8.8	18	8.4	49	8.7
Size (cm), Mean (min-max)	4 (1-18)		4 (0.8-10)		4 (1.2-12)	
Multifocality						
Single	68	19.3	42	19.6	93	16.5
Multiple	7	1.9	6	2.8	12	2.1
No data	277	78.8	166	77.6	458	81.4
Type of surgery						
Biopsy	25	7.1	21	9.8	55	9.7
Mastectomy	110	31.2	61	28.5	170	30.1
No data	217	61.7	132	61.7	338	60.1
Histologic type						
Special	36	10.2	22	10.2	52	9.2
No special type	287	81.5	182	85.1	462	82.1
Mixed	29	8.3	10	4.7	49	8.7
Grade						
1	26	7.5	15	7.1	46	8.2
2	190	53.9	112	52.3	293	52.0
3	136	38.6	87	40.6	224	39.8
Clinical stage						
1	3	0.8	0	0	4	0.7
2	25	7.2	9	4.2	35	6.3
3	45	12.8	21	9.8	95	16.9
4	30	8.5	24	11.2	38	6.7
No data	249	70.7	160	74.8	391	69.4
Hormone receptor						
Positive	265	75.2	194	90.6	491	87.2
Negative	87	24.8	20	9.4	72	12.8
Ki-67						
High (≥ 20%)	181	51.4	103	48.1	257	45.6
Low (< 20%)	150	42.6	98	45.7	297	52.7
No data	21	6	13	6.2	9	1.7
Molecular subtype*						
Luminal A	141	40.1	96	44.8	216	38.3
Luminal B HER2 negative	109	30.9	85	39.7	264	46.8
TNBC	92	26.1	21	9.8	76	13.4
Undetermined	10	2.9	12	5.7	7	1.5

*HER2 status after reassessed

Based on the HER2 assessment data before reclassification, there were 858 cases (75.9%) of HER2-negative breast cancer with no HER2 score listed in the examination report. Of these 858 cases, 711 (82%) were found in 2019 and 147 (18%) in 2020. After reclassification, the distribution of HER2 scores from the 858 cases can be seen in Table 2.

Table 2. Cases of HER2 status without a score before reclassification.

Reclassification	No score		HER2 score							
			0		0-1		1+		2+	
	n	%	n	%	n	%	n	%	n	%
Before	858	100				-				
After	-		308	35.8	176	20.5	299	34.8	75	8.9

A gap in HER2 score assessment before and after reclassification was found. The most frequent score change before and after reclassification was from 1+ to 2+, with 48 cases. The least frequent change was from 0 to 0-1, with 1 case. This discrepancy in scores can be seen in Table 3.

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Table 3. Discrepancy of HER2 scoring before and after reclassification.

HER2 score	Before reclassification		After reclassification		Discrepancy (%)
	n	%	n	%	
0	5	0.4	355	31.4	31
0-1	0	0	214	18.9	18.9
1+	210	18.6	422	37.3	18.7
2+ without amplification	56	5.1	138	12.2	7.1

In this study, the assessment of HER2 expression was conducted with inter-rater reliability analysis using Cohen's Kappa, which yielded a result of 0.82 (very strong agreement).

DISCUSSION

Assessment of HER2 scores in invasive breast carcinoma is crucial. According to the ASCO and CAP guidelines for 2023, HER2-low classification (HER2 score of 1+ and 2+ without amplification) needs to be distinguished from HER2-null (HER2 score 0). This is based on the DESTINY-Breast-04 clinical trial, which showed that treatment with the new drug trastuzumab deruxtecan (T-Dxd) effectively improves overall survival and progression-free survival in patients with HER2-low breast cancer who have metastasized.[7,12-13] Therefore, pathologists are required to report HER2 scores for negative HER2 diagnoses, including scores 0, 1+, and 2+ without HER2 amplification. Scores of 2+ with HER2 amplification and scores of 3+ must be included when diagnosing HER2-positive breast cancer. Data on the classification and clinicopathological features of HER2-negative breast cancer, specifically HER2-null, HER2-low, and ultra-low, are still challenging to find in Indonesia.

In this study, there was no age difference among the three HER2-negative groups, with a median age of 49 years old (ranging from 22 to 88 years old). Emily *et al.*[14] also reported no age difference among HER2-negative groups. The similarity in age among these groups may be due to the significant increase in breast cancer incidence among premenopausal women compared to postmenopausal women. This could be related to the gradual decrease in estrogen production by the ovaries in postmenopausal women.[12] Breast cancer pathogenesis involves various signaling pathways, including hormonal ones. Hormone receptor-positive breast cancer is frequently observed in premenopausal women. In this study, all three HER2-negative groups predominantly expressed hormone receptors. Thus, the age of patients with HER2-negative breast cancer in these groups is consistent with premenopausal women (median age of 49 years old). Other supporting studies by Putri *et al.*[15] have shown that breast cancer is most commonly found in women aged 51-60 years old (46%) and least commonly in women under 30 years old(1%).

The lesions in all three HER2-negative groups were most frequently located in the right breast. This finding aligns with Mehdi *et al.*,[16] who also found that HER2-null and HER2-low lesions were predominantly in the right breast. However, the difference in lesion sites between the right and left breasts was not significant, indicating that both locations have an equal chance of developing lesions.

The average tumor size in this study was 4 cm across all HER2-negative groups. Mehdi *et al.*[16] observed tumors sized 2-5 cm in HER2-null cases and tumors larger than 5 cm in HER2-low cases. The larger tumor sizes observed in their study could be attributed to their focus on TNBC cases, which often have higher proliferation rates compared to hormone-positive cancers.

The lesions in this study were primarily single, which is consistent with Chen *et al.*,[8] who found that 91% of HER2-negative cases had single lesions. The most common surgical procedure to obtain specimens from HER2-negative cases was mastectomy. Shi *et al.*[17] and Chen *et al.*[8] also used mastectomy to obtain breast cancer specimens. The high number of HER2-negative cases with advanced stages (stages 3 and 4) in this study may explain the predominance of mastectomy as the surgical choice. Regardless of tumor size, tumor spread to lymph nodes, chest wall, and distant metastases can increase the stage of breast cancer, leading to mastectomy as the preferred surgical option.

The most common histopathological type found in this study was NST carcinoma. NST carcinoma was the most prevalent type in all three HER2-negative groups. Ling Xin *et al.*,[18] found that 90% of HER2-low cases were NST carcinoma. The broad morphological variability of NST carcinoma and the difficulty in diagnosing special types of carcinoma make

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NST carcinoma the most frequently encountered type in HER2-negative cases. To diagnose special-type carcinomas, the tumor area exhibiting the special morphology must exceed 90%, whereas, in practice, mixed-type carcinoma between NST and special-type carcinomas is more commonly encountered. Additionally, some NST carcinomas express HER2 (15-20%), indicating that HER2-negative NST carcinomas are more frequently found.[19]

In this study, histological grade 2 was most common in HER2-null (53.9%) and HER2-low (52.0%) groups. Histological grade 3 was most common in HER2 ultra-low (40.6%). Daniel *et al.*,[4] reported similar findings, with histological grade 2 being most common in HER2-null and HER2-low groups (44.6% and 48.7%, respectively). Shi *et al.*,[17] also found that HER2 ultra-low cases had the highest proportion of grade 3 histology (32.5%). However, Chen *et al.*,[8] found that HER2-null cases had the highest grade 3 histology, which differs from this study. Despite this, the difference in histological grade among the HER2-negative groups in this study was not statistically significant. Variations in histological grading may be due to differences in the Nottingham grading system used, particularly in scoring mitosis.

The study found a high prevalence of advanced-stage cases. Stages 3 and 4 were most common in HER2-low and ultra-low groups. This may be because Dr.Cipto Mangunkusumo Hospital is a national referral center that frequently receives advanced-stage cases from other hospitals. Studies by Daniel *et al.*,[4] and Yang *et al.*,[20] found that HER2-null and HER2-low cases were more frequently found in the early stages (1 and 2). These studies used secondary data from national cancer registries in their respective countries, where early detection and adequate oncology services lead to earlier breast cancer diagnosis. In contrast, low public awareness and insufficient oncology services in Indonesia contribute to the late detection of breast cancer.[21] As of 2023, Indonesia is classified as a lower-middle-income country. Barrios' study indicated that advanced-stage breast cancer is more common in lower-middle-income countries, whereas early-stage cases are predominantly found in higher-income countries such as the United States.[22]

This study found that all three HER2-negative groups predominantly had hormone receptor-positive tumors. The HER2 ultra-low group had the highest proportion of hormone receptor-positive tumors (90.6%), followed by HER2-low (87.2%) and HER2-null (75.2%). Chen *et al.*,[8] Viale *et al.*,[23] and Wu *et al.*,[24] found that HER2-low cases had more hormone receptor-positive tumors compared to HER2-null cases. Estrogen receptors (ER) can modulate various gene expressions by forming dimers that regulate gene expression. ER can also function as a regulator of other transcription factors. Some receptor tyrosine kinases (RTKs) like epidermal growth factor receptor (EGFR), insulin growth factor-1 (IGF-1), and HER2 can activate ER independently through phosphorylation, creating a combined signaling pathway between ER and RTKs. This combined pathway may explain why HER2-low cases are more frequently found with hormone receptor positivity.[25]

HER2-null cases had the highest proportion of tumors with high Ki-67 status (≥20%) at 51.4%, while HER2-low cases had the highest proportion of tumors with low Ki-67 status (<20%) at 52.7%. This is consistent with Yang *et al.*,[20] who reported high Ki-67 levels (>20%) in HER2-null cases, and Zhang *et al.*,[26] who found low Ki-67 levels (<15%) in HER2-low cases. Ki-67 is a marker of breast cancer proliferation and is important for assessing tumor aggressiveness and determining treatment such as chemotherapy. However, Ki-67 is not universally used due to the lack of consensus on scoring and cut-off values. Tumors with HER2 positivity and TNBC can have Ki-67 values ranging from 30-100%, whereas luminal A tumors typically have low Ki-67 values (less than 15%). The difference in Ki-67 values between HER2-null and HER2-low cases may be due to different mutations. Wei *et al.*,[27] found that HER2-low cases more often have mutations in phosphatidylinositol 3-kinase/protein kinase B compared to p53 mutations, while HER2-null cases more often have p53 mutations. Further research is needed to verify these mutations between the two groups.

Among HER2-negative cases, the most common molecular subtype was luminal B HER2-negative (40.5%), while the least common was TNBC (16.7%). The HER2-low group had the highest proportion of luminal B HER2-negative subtype (46.8%). This is

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consistent with You *et al.*,[28] who found HER2-low cases to be predominantly luminal B (57.4%).

Thirteen percent of HER2-low cases were TNBC. Despite the small number, these cases are eligible for the new ADC therapies, provided the clinical condition is appropriate, such as the presence of metastasis. Currently, TNBC is treated with chemotherapy. The 2021 TNBC management guidelines by Bou Zerdan *et al.*,[29] suggest that ADCs like sacituzumab govitecan can be used as a second-line treatment for metastatic TNBC. Patients receiving sacituzumab govitecan showed improved progression-free survival (4.8 months vs. 1.7 months) and overall survival (11.8 months vs. 6.9 months) compared to those receiving chemotherapy.

This retrospective study found that the most frequent change in HER2 scores after reclassification was from 1+ to 2+. This may be due to inter-observer variability in assessing HER2 staining intensity, completeness of staining on the membrane, and the extent of invasive tumor area on HER2 slides, all evaluated under a light microscope. Such variability can lead to differences in HER2 scores among observers.

There are several limitations in this study. Clinical data such as lesion location, lesion size, lesion multifocality, clinical stage, and type of surgical procedure are mostly unavailable in the examination forms from the archives of the Anatomical Pathology Department at Dr. Cipto Mangunkusumo Hospital, as well as in the hospital's electronic medical records. In addition to the clinical data, information on Ki-67 status was also unavailable for certain periods due to a shortage of Ki-67 antibody reagents at that time. Furthermore, some cases that had their HER2 scores changed to 2+ after reclassification were not followed up with ISH testing to assess HER2 gene amplification status.

In conclusion, the highest number of HER2-negative KPI cases at the Anatomical Pathology Department of RSCM for the years 2019-2020 was found in the HER2-low group (49.8%), followed by the HER2-null group (31.3%), and the HER2 ultra-low group (18.9%). There were no significant differences in average age and tumor size among the three HER2-negative KPI groups. HER2 ultra-low cases were most commonly found in the right breast, as single lesions, with histopathological type NST carcinoma, and had positive hormone receptors. The majority of HER2-null specimens were obtained from mastectomy results, with histological grade 2 and high Ki-67 status (> 20%). HER2-low cases were most frequently found in clinical stage 3 with a luminal B HER2-negative molecular subtype. There were 855 HER2-negative KPI cases without HER2 scores. The most common score change after reclassification was from 1+ to 2+.

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Conflict of Interest

The authors do not have any conflict of interest to disclose.

Authors Contribution

The authors contributed equally to the research.

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